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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,466	06/20/2001	Arthur L. Herbst	58532-012	9630

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MCDERMOTT WILL & EMERY
600 13TH STREET, N.W.
WASHINGTON, DC 20005-3096

EXAMINER
KIM, VICKIE Y

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/884,466	Applicant(s) HERBST ET AL.	
	Examiner Vickie Kim	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application

1. Claims 1-12 are pending and presented for the prosecution on the merit.

Response to Arguments

1. Applicant's arguments with respect to claims 1-9 have been considered but are moot in view of the new ground(s) of rejection due to the changes made in the newly filed amendment(Paper No. 7).

Claim Objections

2. Claim 1 is objected to because of the following informalities: There is typographical error was found where the word "effects" is omitted right after "side". The proper term should be "side effects". Appropriate correction is required.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Adawi et al(1998).

Adawi et al teach a method of treating radiation-induced pneumonitis and fibrosis by using monoclonal anti-CD40L antibody(MR1) via blocking Cox-2 expression, see page 229, ..." the effectiveness of MR1 may be due... to block Cox-2 expression.....".

Adawi also teaches that MR1 greatly reduces COX-2 expression. Therefore, one would have envisaged that MRI is properly considered as a selective COX-2 inhibitor in broad sense and thus, the subject matter recited in broad claim 1 is encompassed by the teaching of this cited reference.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1, 3 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over and Kishi et al (March 2000) in view of Maity et al(1998) .

Kishi et al teach an enhancement of radiotherapy using selective COX-2 inhibitors(i.e. celecoxib). They teach that this COX-2 inhibitor(e.g. 6mg/kg given in drinking water) potentiates antitumor efficacy of radiation without increasing radiation injury to normal tissue. They further teach remarkable irradiation doses reduction in the treatment(see page 1327, 4th paragraph and figure 1-B). Thus, one would have been envisaged that a selective COX-2 inhibitors would reduce unwanted side effects caused by radiation therapy. tissue.

However, applicant's claims are still differ because they require specific types of side effects(e.g.dermatitis, fatigue, etc).

It would have been, however, obvious to one of ordinary skill in the art to extend Kishi et al's teaching into all types of radiation therapy to reduce side effects such as pneumonitis taken in view of Maity et al because Maity et al teach that side effects (e.g. pneumonitis) is resulted from radiation induced injury(apoptosis) of normal tissue and it could be prevented by manipulation of radiosensitivity.

Thus, one would have been motivated to do so because a select selective COX-2 inhibitors(e.g.celecoxib) in combination with radiation therapy can reduce unwanted side effects caused by raditaiton therapy by protecting normal tissue via potentiating antitumor efficacy of radiation without increasing radiation injury to normal tissue. One would have been motivated to do so with reasonable expectation of success because reduction of unwanted side effects can be achieved by not only protecting normal tissue but also lowering the radiation doses. Kish et al have proven the effectiveness of selective COX-2 inhibitors on protecting normal tissue from radiation therapy and it is well known and recognized in the art that side effects are related to the radiation doses used as evidenced by numerous documents(PTO-892). In other words, treatment requires less radiation to achieve same therapeutic outcome and less side effects are expected. Therefore, one would optimize successful radiation therapy by adding selective COX-2 inhibitor into the therapy so that one would maximize the therapeutic effectiveness while lowering unwanted side effects(e.g. pneumonitis) associated with radiation therapy.

3. Claims 2, 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kishi et al (March 2000) in view of Maity et al(1998) mentioned above, further in view of Ducharme et al (US patent 5,474,995) or Weichselbaum et al(US patent 5,641,755).

As mentioned earlier (supra), Kishi in view of Maity teach the method of treating side effect which occurs with radiation therapy using selective COX-2 inhibitors.

The claim 2 differs in that a specific COX-2 inhibitor is required, namely rofecoxib.

However, Ducharme et al teach 3-phenyl-4-(4-(methylsulfonyl)phenyl-2-(5H)-furanone as a selective COX-2 inhibitor (see claim 14). It is noted that rofecoxib's chemical name is 3-phenyl-4-(4-(methylsulfonyl)phenyl-2-(5H)-furanone. Thus, it would have been obvious to one of ordinary skill in the art to substitute rofecoxib to the selective COX-2 inhibitors(e.g. celecoxib) in Kishi's refernece to achieve same therapeutic effect because extension of therapeutic modality is always desired and they are proven to be effective selective COX-2 inhibitors.

In regarding claims 4-6, the claims 4-6 differ because they require various side effects (e.g. acute mucosal effect, fatigue, diarrhea, urinary frequency, dermatitis, respectively) and claim 8 requires specific location of the radiation therapy (i.e. outside the pelvis).

However, it would have been obvious to one of ordinary skill in the art to incorporate Weichselbaum's teaching to reduce mucositis, fatigue, diarrhea, urinary frequency or dermatitis because the deficiency is satisfied when they are taken together.

Weichselbaum et al disclose particularly relative teaching regarding radiation-induced side effects (i.e. mucositis, dermatitis or proctitis). Weichselbaum states that radiation-induced side effects could be effectively reduced by regulating metabolic signaling pathway(e.g. arachidonic pathway). Weichselbaum also teaches various radiation exposures to different locations to treat specific tumors (e.g. oropharyngeal mucosa, ultraviolet radiation to skin, etc (see column 7)). Weichselbaum further states that cycloxygenase inhibition may have beneficial role by reducing the production of prostaglandin E2(PGE2), see column 6, lines 60-65. Kishi's reference also teaches same mechanism wherein a selective COX-2 inhibitor effectively inhibits PGE2(see Kishi's, page 1329).

Thus, when these references are taken together, one would have been motivated to add selective COX-2 inhibitor into radiation treatment to reduce the deleterious side effects(e.g. dermatitis, mucositis, etc) because selective COX-2 inhibitors are not only modulating prostaglandin/arachidonic pathway, eventually attenuating inflammatory cytokines(TNF-α or IL-1) production, but also potentiating tumor response to cytotoxic agent and lowering the dose of the radiation.

With respect to claims 5 and 7, they require fatigue and urinary frequency and are properly included in this rejection because it is well known in the art that fatigue or urinary frequency are also radiation induced side effect mediated by prostaglandin pathway induced inflammation evidenced by documents enclosed in PTO-892.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same (or

similar) ingredients and share common utilities, and pertinent to the problem which applicant is concerning. MPEP 2141.01(a).

Conclusion

4. All the pending claims 1-12 are rejected. No claims allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is 703-305-1675. The examiner can normally be reached on Tuesday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on 703-308-4725. The fax phone numbers for the organization where

this application or proceeding is assigned are 703-746-3165 for regular communications and 703-746-3165 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Vickie Kim,

Patent examiner

January 24, 2003

Art unit 1614

William Jarvis

Primary Patent examiner